

**REMARKS**

**THE CLAIM AMENDMENTS**

Applicants have withdrawn claims 1-5 and 10-19 and added claims 20-21. Following entry of this amendment claims 6-9 and 20-21 will be pending.

Applicants have amended claims 8 and 9 to recite proper claim dependencies.

Applicant has added claims 20-21 to recite specific embodiments of the invention. Support for new claims 20 and 21 is provided throughout the specification (see, e.g., pp. 37-41).

None of the amendments introduces any new matter.

**THE RESTRICTION REQUIREMENT**

The Examiner has required restriction of the claims of this application under 35 U.S.C. § 121 into one of the following 37 groups.

Group I: Claims 1-5, to the extent that they are drawn to a biologically active TGF- $\beta$  superfamily member fusion protein comprising a heterologous tissue targeting domain that binds to a cell surface molecule on an osteoprogenitor cell;

Group II: Claims 1-5, to the extent that they are drawn to a biologically active TGF- $\beta$  superfamily member fusion protein comprising a heterologous tissue targeting domain that binds to a cell surface molecule on a chondrocyte;

Group III: Claims 1-5, to the extent that they are drawn to a biologically active TGF- $\beta$  superfamily member fusion protein comprising a molecular targeting domain;

Group IV: Claims 1-5, to the extent that they are drawn to a biologically active TGF- $\beta$  superfamily member fusion protein comprising a heterologous metal binding domain;

Group V: Claims 1-5, to the extent that they are drawn to a biologically active TGF- $\beta$  superfamily member fusion protein comprising a heterologous protein binding domain;

Group VI: Claims 1-5, to the extent that they are drawn to a biologically active TGF- $\beta$  superfamily member fusion protein comprising a heterologous ceramic binding domain;

Group VII: Claims 1-5, to the extent that they are drawn to a biologically active TGF- $\beta$  superfamily member fusion protein comprising a heterologous HAP binding domain;

Group VIII: Claims 1-5, to the extent that they are drawn to a biologically active TGF- $\beta$  superfamily member fusion protein comprising a heterologous collagen domain;

Group IX: Claim 6-8 to the extent that they are drawn to a latent TGF- $\beta$  family member comprising a cleavable leader sequence;

Group X: Claim 6-9, to the extent that they are drawn to a latent TGF- $\beta$  family member comprising a heterologous cleavable leader sequence;

Group XI: Claims 10-16, to the extent that they are drawn to a biologically active TGF- $\beta$  family member comprising a truncated leader sequence;

Group XII: Claim 17, to the extent that it is drawn to a biologically active heterodimer of TGF- $\beta$  family member proteins comprising a first subunit being a TGF- $\beta$  family member fusion protein, and a second subunit comprising a TGF- $\beta$  family member fusion protein different from that of the first subunit;

Group XIII: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF- $\beta$  family member proteins comprising a first subunit being a TGF- $\beta$  family member fusion protein, and a second subunit comprising a wild type TGF- $\beta$ 1 subunit;

Group XIV: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF- $\beta$  family member proteins comprising a first subunit being a TGF- $\beta$  family member fusion protein, and a second subunit comprising a wild type TGF- $\beta$ 2 subunit;

Group XV: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF- $\beta$  family member proteins comprising a first subunit being a TGF- $\beta$  family member fusion protein, and a second subunit comprising a wild type TGF- $\beta$ 3 subunit;

Group XVI: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF- $\beta$  family member proteins comprising a first subunit being a TGF- $\beta$  family member fusion protein, and a second subunit comprising a wild type TGF- $\beta$ 4 subunit;

Group XVII: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF- $\beta$  family member proteins comprising a first subunit being a TGF- $\beta$  family member fusion protein, and a second subunit comprising a wild type TGF- $\beta$ 5 subunit;

Group XVIII: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF- $\beta$  family member proteins comprising a first subunit being a TGF- $\beta$  family member fusion protein, and a second subunit comprising a wild type dpp subunit;

Group XIX: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF- $\beta$  family member proteins comprising a first subunit being a TGF- $\beta$  family member fusion protein, and a second subunit comprising a wild type Vg-1 subunit;

Group XX: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF- $\beta$  family member proteins comprising a first subunit being a TGF- $\beta$  family member fusion protein, and a second subunit comprising a wild type Vgr-1 subunit;

Group XXI: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF- $\beta$  family member proteins comprising a first subunit being a TGF- $\beta$  family member fusion protein, and a second subunit comprising a wild type 60A subunit;

Group XXII: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF- $\beta$  family member proteins comprising a first subunit being a TGF- $\beta$  family member fusion protein, and a second subunit comprising a wild type BMP-2A subunit;

Group XXIII: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF- $\beta$  family member proteins comprising a first subunit being a TGF- $\beta$  family member fusion protein, and a second subunit comprising a wild type BMP-3 subunit;

Group XXIV: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF- $\beta$  family member proteins comprising a first subunit being a TGF- $\beta$  family member fusion protein, and a second subunit comprising a wild type BMP-4 subunit;

Group XXV: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF- $\beta$  family member proteins comprising a first subunit being a TGF- $\beta$  family member fusion protein, and a second subunit comprising a wild type BMP-5 subunit;

Group XXVI: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF- $\beta$  family member proteins comprising a first subunit being a TGF- $\beta$  family member fusion protein, and a second subunit comprising a wild type BMP-6 subunit;

Group XXVII: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF- $\beta$  family member proteins comprising a first subunit being a TGF- $\beta$  family member fusion protein, and a second subunit comprising a wild type dorsalin subunit;

Group XXVIII: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF- $\beta$  family member proteins comprising a first subunit being a TGF- $\beta$  family member fusion protein, and a second subunit comprising a wild type OP-1 subunit;

Group XXIX: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF- $\beta$  family member proteins comprising a first subunit being a TGF- $\beta$  family member fusion protein, and a second subunit comprising a wild type OP-2 subunit;

Group XXX: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF- $\beta$  family member proteins comprising a first subunit being a TGF- $\beta$  family member fusion protein, and a second subunit comprising a wild type OP-3 subunit;

Group XXXI: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF- $\beta$  family member proteins comprising a first subunit being a TGF- $\beta$  family member fusion protein, and a second subunit comprising a wild type GDF-1 subunit;

Group XXXII: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF- $\beta$  family member proteins comprising a first subunit being a TGF- $\beta$  family member fusion protein, and a second subunit comprising a wild type GDF-3 subunit;

Group XXXIII: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF- $\beta$  family member proteins comprising a first subunit being a TGF- $\beta$  family member fusion protein, and a second subunit comprising a wild type GDF-9 subunit;

Group XXXIV: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF- $\beta$  family member proteins comprising a first subunit being a TGF- $\beta$  family member fusion protein, and a second subunit comprising a wild type Inhibin  $\beta$  subunit;

Group XXXV\*: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF- $\beta$  family member proteins comprising a first subunit being a TGF- $\beta$  family member fusion protein, and a second subunit comprising a wild type Inhibin  $\beta$ A subunit;

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\* The Examiner recited this group as Group XXXIV. Applicant believes that the Examiner intended this group to be XXXV and all subsequent groups to be one number greater than that recited in the Restriction Requirement.

Group XXXVI: Claims 17 and 18 to the extent that they are drawn to a biologically active heterodimer of TGF- $\beta$  family member proteins comprising a first subunit being a TGF- $\beta$  family member fusion protein, and a second subunit comprising a wild type Inhibin  $\beta$ B subunit; and

Group XXXVII: Claims 19, drawn to a method of purifying a heterodimer of TGF- $\beta$  family proteins.

The Examiner asserts that the inventions encompassed by Groups I-XXXVII are patentably distinct from one another and have acquired a separate status in the art. The Examiner states that the inventions encompassed by the following pairwise combinations of products are independent and distinct, wherein neither member of a pair is required for the production or use of the other, and wherein each of the pair can be manufactured independently of the other and used for independent and distinct purposes: Group I and each of Groups II-XXXV; Group II and each of Groups III-XXXV; Group III and each of Groups IV-XXXV; Group IV and each of Groups V-XXXV; Group V and each of Groups VI-XXXV; Group VI and each of Groups VII-XXXV; Group VII and each of Groups VIII-XXXV; Group VIII and each of Groups IX-XXXV; Group IX and each of Groups X-XXXV; Group X and each of Groups XI-XXXV; Group XI and each of Groups XII-XXXV; Group XII and each of Groups XIII-XXXV; Group XIII and each of Groups XIV-XXXV; Group XIV and each of Groups XV-XXXV; Group XV and each of Groups XVI-XXXV; Group XVI and each of Groups XVII-XXXV; Group XVII and each of Groups XVIII-XXXV; Group XVIII and each of Groups XIX-XXXV; Group XIX and each of Groups XX-XXXV; Group XX and each of Groups XXI-XXXV; Group XXI and each of



Groups XXII-XXXV; Group XXII and each of Groups XXIII-XXXV; Group XXIII and each of Groups XXIV-XXXV; Group XXIV and each of Groups XXV-XXXV; Group XXV and each of Groups XXVI-XXXV; Group XXVI and each of Groups XXVII-XXXV; Group XXVII and each of Groups XXVIII-XXXV; Group XXVIII and each of Groups XXIX-XXXV; Group XXIX and each of Groups XXX-XXXV; Group XXX and each of Groups XXXI-XXXV; Group XXXI and each of Groups XXXII-XXXV; Group XXXII and each of Groups XXXIII-XXXV; Group XXXIII and each of Groups XXXIV-XXXV; Group XXXIV and Group XXXV. The Examiner further states that inventions XXXVI and each of I-XXXV are related as process of making and product made\*.

Applicants traverse the restriction of Groups I-XXXVII and submit that the restriction is improperly drawn.

The Manual of Patent Examining Procedure (MPEP) states that there are two criteria for a proper requirement of restriction between patentably distinct inventions. The first is that the inventions must be independent or distinct as claimed. The second is that there must be a serious burden on the Examiner if restriction is not required. The MPEP further states that "[i]f the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to distinct or independent inventions." MPEP § 803.

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\* The Examiner has recited Group XXXIV twice. Applicant believes that each group beyond Group XXXIV recited by the Examiner is intended to be one number greater than that recited. Thus, applicant believes that the Examiner intended to recite 37 groups (i.e., up to Group XXXVII).

Applicants request that Groups IX and X be examined together. A search for groups IX is co-extensive with that for group X and the two searches could be carried out simultaneously. Thus, there would be no serious search burden on the Examiner if Group IX and X are examined together. Applicants, therefore, respectfully request that the Examiner consider Group IX and X together.

If the Examiner does not agree with applicants' proposal to rejoin Groups IX and X, applicants provisionally elect with traverse Group IX for initial substantive examination. 37 C.F.R. § 1.143. This election is made expressly without waiver of applicants' rights to continue to prosecute and to obtain claims to the non-elected and/or canceled subject matter either in this application or in other applications claiming priority herefrom.

### **CONCLUSION**

Applicants request consideration of the application and early allowance of the pending claims.

Respectfully submitted,



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